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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/608,354	06/27/2003	Stanley T. Crook	MSIBIS-0002USC2	2899
27180	7590	01/02/2009		
ISIS PHARMACEUTICALS INC 1896 RUTHERFORD RD. CARLSBAD, CA 92008			EXAMINER LU, FRANK WEI MIN	
			ART UNIT 1634	PAPER NUMBER
			MAIL DATE 01/02/2009	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/608,354

**Applicant(s)**

CROOK ET AL.

**Examiner**

FRANK W. LU

**Art Unit**

1634

**Period for Reply** -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 01 October 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 38, 39, 95, 97-99, 101, 103, 104 and 109-114 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 38, 39, 95, 97-99, 101, 103, 104 and 109-114 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 03 January 2008 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 10/1/2008
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Response to Amendment***

1. Applicant's response to the office action filed on October 1, 2008 has been entered. The claims pending in this application are claims 38, 39, 95, 97-99, 101, 103, 104, and 109-114. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of applicant's amendment filed on October 1, 2008.

### ***Specification***

2. The disclosure is objected to because of the following informality: it is unclear that the word "which" in the phrase "the disclosure of which is incorporated herein by reference in its entirety" in line 5 of the amended specification (see page 2 of applicant's remarks) means U.S. Patent No. 6,656,690, U.S. Patent No. 6,329,146, and U.S. Patent No. 6,428,956 or only means U.S. Patent No. 6,428,956.

Appropriate correction is required.

### ***Sequencing Listing***

3. The sequencing listing filed on October 1, 2008 has been accepted by the office.

### ***Claim Objections***

4. Claim 111 is objected to because of the following informality: "combining with said complex a mixture of compounds" in step (c) should be "combining said complex with a mixture of compounds".

Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 38, 39, 95, 97-99, 101, 103, 104, and 109-114 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
7. Claim 111 is rejected as vague and indefinite. Since step (f) does not indicate how binding of one or more members of said mixture of compounds is related to at least one mass to charge ratio obtained in step (e), it is unclear why whether binding of one or more members of said mixture of compounds to the nucleic acid target has occurred can be determined by comparing at least one mass to charge ratio obtained in step (e) to the known mass to charge ratio of the complex. Please clarify.
8. Claim 111 is rejected as vague and indefinite. Since step (c) does not indicate that one or more members in a mixture of compounds have known identities, it is unclear why the identity of said one or more members can be determined by calculating the mass of said one or more members as recited in step (g). Please clarify.
9. Claim 113 is rejected as vague and indefinite. Since the claim does not indicate how to calculate a relative dissociation constant for said member by comparing the ion abundance of said one or more members to the known ion abundance of the complex, it is unclear why a relative dissociation constant for said member can be determined by comparing the ion abundance of said one or more members to the known ion abundance of the complex. Please clarify.

***Response to Arguments***

In page 7, last paragraph bridging to page 8, first paragraph of applicant's remarks, applicant argues that "[C]laim 111 also stands rejected allegedly being vague and indefinite because step (f), (g) and (h) are unclear as to 'why' or 'whether' they would achieve each of their asserted objectives. Applicants respectfully submit that such rejections of claim 111 are inappropriate because the Examiner is questioning the veracity of the claimed steps and what they are intended to achieve. In addition, implied in the rejection, is a questioning of the veracity of the claimed invention in view of the description provided by the Applicants. In the specification as filed, the Applicants provide one of ordinary skill in the art an abundance of guidance, including 22 examples and 33 figures, as to how to perform the claimed methods. Applicants respectfully submit that one of ordinary skill in the art would appreciate how, in view of the extensive specification, each of these steps would achieve each of their stated objectives".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, since step (f) of claim 111 does not indicate how binding of one or more members of said mixture of compounds is related to at least one mass to charge ratio obtained in step (e), it is unclear why whether binding of one or more members of said mixture of compounds to the nucleic acid target has occurred can be determined by comparing at least one mass to charge ratio obtained in step (e) to the known mass to charge ratio of the complex. Second, since step (c) of claim 111 does not indicate that one or more members in a mixture of compounds have known identities, it is unclear why the identity of said one or more members can be determined by calculating the mass of said one or more members as recited in step (g). Third, since claim 113 (previous step (h) of claim 111) does not indicate how to calculate a

relative dissociation constant for said member by comparing the ion abundance of said one or more members to the known ion abundance of the complex, it is unclear why a relative dissociation constant for said member can be determined by comparing the ion abundance of said one or more members to the known ion abundance of the complex. Fourth, applicant's arguments appear to argue the rejections under 35 U.S.C. 112, first paragraph (enablement). However, above rejections are under 35 U.S.C. 112, second paragraph and are not under 35 U.S.C. 112, first paragraph (enablement).

10. Claim 112 is rejected as vague and indefinite. Since step (g) does not indicate how binding of one or more members of said mixture of compounds is related to the mass to charge ratio collected in steps (c) and (f), it is unclear why whether binding of one or more members of said mixture of compounds to the nucleic acid target has occurred can be determined by comparing the mass to charge ratio collected in steps (c) and (f). Please clarify.

11. Claim 112 is rejected as vague and indefinite. Since step (d) does not indicate that one or more members in a mixture of compounds have known identities, it is unclear why the identity of said one or more members can be determined by calculating the mass of said one or more members as recited in step (h). Please clarify.

12. Claim 114 is rejected as vague and indefinite. Since the claim does not indicate how to calculate a relative dissociation constant for said member by comparing the ion abundance of said one or more members to the known ion abundance of the complex, it is unclear why a relative dissociation constant for said member can be determined by comparing the ion

abundance of said one or more members to the known ion abundance of the complex. Please clarify.

***Response to Arguments***

In page 8, second paragraph of applicant's remarks, applicant argues that "[C]laim 112 also stands rejected allegedly being vague and indefinite because step (g), (h) and (i) are unclear as to 'why' or 'whether' they would achieve each of their asserted objectives. Applicants respectfully submit that such rejections of claim 112 are inappropriate because the Examiner is questioning the veracity of the claimed steps and what they are intended to achieve. In addition, implied in the rejection, is a questioning of the veracity of the claimed invention in view of the description provided by the Applicants. In the specification as filed, the Applicants provide one of ordinary skill in the art an abundance of guidance, including 22 examples and 33 figures, as to how to perform the claimed methods. Applicants respectfully submit that one of ordinary skill in the art would appreciate how, in view of the extensive specification, each of these steps would achieve each of their stated objectives".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, since step (g) does not indicate how binding of one or more members of said mixture of compounds is related to the mass to charge ratio collected in steps (c) and (f), it is unclear why whether binding of one or more members of said mixture of compounds to the nucleic acid target has occurred can be determined by comparing the mass to charge ratio collected in steps (c) and (f). Second, since step (d) does not indicate that one or more members in a mixture of compounds have known identities, it is unclear why the identity of said one or more members can be determined by calculating the mass of said one or more

members as recited in step (h). Third, claim 114 (previous step (i) of claim 112) does not indicate how to calculate a relative dissociation constant for said member by comparing the ion abundance of said one or more members to the known ion abundance of the complex, it is unclear why a relative dissociation constant for said member can be determined by comparing the ion abundance of said one or more members to the known ion abundance of the complex. Fourth, applicant's arguments appear to argue the rejections under 35 U.S.C. 112, first paragraph (enablement). However, above rejections are under 35 U.S.C. 112, second paragraph and are not under 35 U.S.C. 112, first paragraph (enablement).

### ***Conclusion***

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. No claim is allowed.



15. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

/Frank W Lu /  
Primary Examiner, Art Unit 1634  
December 30, 2008